

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To: KAREN L. ELBING
CLARK & ELBING LLP
176 FEDERAL STREET
BOSTON MA 02110-2214

RECEIVED

FEB 26 2002

Date of Mailing
(day/month/year)

14 FEB 2002

Applicant's or agent's file reference
00786/381WO2

REPLY DUE

within **ONE** months
from the above date of mailing

International application No.

PCT/US01/01212

International filing date (day/month/year)

12 JANUARY 2001

Priority date (day/month/year)

12 JANUARY 2000

International Patent Classification (IPC) or both national classification and IPC
IPC(7): C12Q 1/68; A 61K 48/00; C 12N 15/00 and US Cl.: 435/6; 514/44; 800/21

Applicant

THE GENERAL HOSPITAL CORPORATION

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

ACTION DUE

DUE DATE

INITIALS

Reply to Written Opinion

3-14-02

J.M.

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 12 MAY 2002

Name and mailing address of the IPEA/US
Commissioner of Patents and Trademarks
Form PCT/IPC (see sheet) (July 1998)*
Washington, DC 20531

Authorized officer

JEHANNE SOULET 308-1235

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To: KAREN L. ELBING CLARK & ELBING LLP 176 FEDERAL STREET BOSTON MA 02110-2214		Date of Mailing (day/month/year) 14 FEB 2002	
Applicant's or agent's file reference 00786/381WO2		REPLY DUE within ONE months from the above date of mailing	
International application No. PCT/US01/01212	International filing date (day/month/year) 12 JANUARY 2001	Priority date (day/month/year) 12 JANUARY 2000	
International Patent Classification (IPC) or both national classification and IPC IPC(7): C12Q 1/68; A 61K 48/00; C 12N 15/00 and US Cl.: 435/6; 514/44; 800/21			
Applicant THE GENERAL HOSPITAL CORPORATION			

1. This written opinion is the <u>first</u> (first, etc.) drawn by this International Preliminary Examining Authority.	
2. This opinion contains indications relating to the following items: <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step or industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 	
3. The applicant is hereby invited to reply to this opinion. <p>When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).</p> <p>How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.</p> <p>Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6.</p> <p>If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.</p>	
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: <u>12 MAY 2002</u>	

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Form PCT/IPC/US (July 1998)* Washington, D.C. 20231	Authorized officer JEHANNE SOYAK <i>[Signature]</i>
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WRITTEN OPINION

International application No.

PCT/US01/01212

I. Basis of the opinion

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☒ the description:
 pages 1-29 , as originally filed
 pages NONE , filed with the demand
 pages NONE , filed with the letter of

- ☒ the claims:
 pages 30-32 , as originally filed
 pages NONE , as amended (together with any statement) under Article 19
 pages NONE , filed with the demand
 pages NONE , filed with the letter of

- ☒ the drawings:
 pages 1-1 , as originally filed
 pages NONE , filed with the demand
 pages NONE , filed with the letter of

- ☒ the sequence listing part of the description:
 pages 1-79 , as originally filed
 pages NONE , filed with the demand
 pages NONE , filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
 These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages none
- ☒ the claims, Nos. none
- ☒ the drawings, sheets/fig none

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

WRITTEN OPINION

International application No.

PCT/US01/01212

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	<u>7-13 and 15-19</u>	YES
	Claims	<u>1-6, 14</u>	NO
Inventive Step (IS)	Claims	<u>7-13, and 15-19</u>	YES
	Claims	<u>1-6, 14</u>	NO
Industrial Applicability (IA)	Claims	<u>1-19</u>	YES
	Claims	<u>none</u>	NO

2. citations and explanations

Claims 1-6 lack novelty under PCT Article 33(2) as being anticipated by Satoh et al.

Satoh teaches that a G to T transversion of codon 740, exon 14, of the titin gene, replacing Arginine with Leucine, was found in patient with hypertrophic cardiomyopathy (HCM) and not in 500 normal chromosomes (see abstract). Satoh teaches that this mutation may cause HCM in the patient via altered affinity to alpha actinin (see abstract). Satoh teaches PCR amplification with titin specific primers as well as sequence analysis of the exon 14 mutation (see p. 412).

Claim 14 lacks novelty under PCT Article 33(2) as being anticipated by Jackel et al..

Jackel teaches a mutation in the titin gene found in a baby hamster kidney cell line. Jackel teaches that the mutation involved missing extended sequences coding for Z-line associated domains (see abstract).

Claims 7-13 and 15-19 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest determining whether a subject has or is at risk of developing a titin related disease or condition wherein the mutation is the pickwick mutation. The prior art does not teach or fairly suggest identifying compounds that can be used to treat or prevent heart failure by contacting an organism with a titin mutation with a test compound. The prior art does not teach or fairly suggest a zebra fish with a mutation in the titin gene, or any non human animal with a mutation in a cardiac specific exon of the titin gene or the N2B exon of the titin gene or a mutation which results in the presence of a stop codon in the titin gene, or the pickwick mutation in the titin gene.

Claims 1-19 meet the criteria set out under PCT Article 33(4) for Industrial Applicability.
(Continued on Supplemental Sheet.)

WRITTEN OPINION

International application No.

PCT/US01/01212

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

----- NEW CITATIONS -----

JACKEL M. et al. Deletion in the Z-line Region of the Titin Gene in a Baby Hamster Kidney Cell Line, BHK-21-Bi. Febs Letters. 12 May 1997. Vol 308. pages 21-24, see abstract.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To: KAREN L. ELBING CLARK & ELBING LLP 176 FEDERAL STREET BOSTON MA 02110-2214	<div style="text-align: right; margin-bottom: 10px;"> <i>7/14/01</i> <i>16 MAY 2001</i> </div> <div style="border: 1px solid black; padding: 2px;"> Date of Mailing (day/month/year) </div>
Applicant's or agent's file reference 00786/381WO2	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US01/01212	International filing date (day/month/year) 12 JANUARY 2001
Applicant THE GENERAL HOSPITAL CORPORATION	

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.
Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.
2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.
4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in rules 90 bis 1 and 90 bis 3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JEHANNE SOUAYA Telephone No. (703) 308-1235
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TERRY J. DEY
PARALEGAL SPECIALIST
TECHNOLOGY CENTER 1600

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 00786/381WO2	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/US01/01212	International filing date (day/month/year) 12 JANUARY 2001	(Earliest) Priority Date (day/month/year) 12 JANUARY 2000
Applicant THE GENERAL HOSPITAL CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☐ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
- ☒ the text is approved as submitted by the applicant.
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No. _____
- ☐ as suggested by the applicant.
- ☐ because the applicant failed to suggest a figure.
- ☐ because this figure better characterizes the invention.
- ☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/01212

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12Q 1/68; A61K 48/00; C12N 15/00

US CL : 435/6; 514/44; 800/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/6; 514/44; 800/21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, caplus, medline, uspatful

search terms: titin gene, mutation, pickwick, heart disease, cardiac, cardio?, zebrafish

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- A	SATOH. M. Structural Analysis of the Titin Gene in Hypertrophic Cardiomyopathy: Identification of a Novel Disease Gene. Biochemical and Biophysical Research Communications. August 1999. Vol 262. pages 411-417, especially abstract, page 412, Fig.3, page 414.	1-6 ----- 7-19
A	SIU. B.L. Familial Dilated Cardiomyopathy Locus Maps to Chromosome 2q31. Circulation. 02 March 1999. Vol 99. pages 1022-1026, especially abstract, Fig. 3.	1-19

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

26 FEBRUARY 2001

Date of mailing of the international search report

16 MAY 2001

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

JEHANNE SOUAYA

Telephone No.

(703) 308-1233

TERRY J. DEY
PARALEGAL SPECIALIST
TECHNOLOGY CENTER 1600